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Comparison of Outcomes of HLA-Matched Related, Unrelated, or HLA-Haploidentical Related Hematopoietic Cell Transplantation following Nonmyeloablative Conditioning for Relapsed or Refractory Hodgkin Lymphoma

Lauri M. Burroughs,[1] Paul V. O'Donnell,[1] Brenda M. Sandmaier,[1] Barry E. Storer,[1] Leo Luznik,[2] Heather J. Symons,[2] Richard J. Jones,[2] Richard F. Ambinder,[2] Michael B. Maris,[3] Karl G. Blume,[4] Dietger W. Niederwieser,[5] Benedetto Bruno,[6] Richard T. Maziarz,[7] Michael A. Pulsipher,[8] Finn B. Petersen,[9] Rainer Storb,[1] Ephraim J. Fuchs,[2] David G. Maloney[1]

We compared the outcome of nonmyeloablative allogeneic hematopoietic cell transplantation (HCT) for patients with relapsed or refractory Hodgkin lymphoma (HL) based on donor cell source. Ninety patients with HL were treated with nonmyeloablative conditioning followed by HCT from HLA-matched related, n = 38, unrelated, n = 24, or HLA-haploidentical related, n = 28 donors. Patients were heavily pretreated with a median of 5 regimens and most patients had failed autologous HCT (92%) and local radiation therapy (83%). With a median follow-up of 25 months, 2-year overall survivals, progression-free survivals (OS)/(PFS), and incidences of relapsed/progressive disease were 53%, 23%, and 56% (HLA-matched related), 58%, 29%, and 63% (unrelated), and 58%, 51%, and 40% (HLA-haploidentical related), respectively. Nonrelapse mortality (NRM) was significantly lower for HLA-haploidentical related ($P = .02$) recipients compared to HLA-matched related recipients. There were also significantly decreased risks of relapse for HLA-haploidentical related recipients compared to HLA-matched related ($P = .01$) and unrelated ($P = .03$) recipients. The incidences of acute grades III-IV and extensive chronic graft-versus-host disease (aGVHD, cGVHD) were 16%/50% (HLA-matched related), 8%/63% (unrelated), and 11%/35% (HLA-haploidentical related). These data suggested that salvage allogeneic HCT using nonmyeloablative conditioning provided antitumor activity in patients with advanced HL; however, disease relapse/progression continued to be major problems. Importantly, alternative donor stem cell sources are a viable option.

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INTRODUCTION

Most patients with Hodgkin lymphoma (HL) are cured with conventional chemotherapy ± radiation therapy. However, 10% to 20% of patients with advanced HL will not achieve complete remission following first-line therapy, and 20% to 30% of patients will relapse following complete remission [1]. Patients with relapsed or refractory disease are often offered salvage treatment with additional intensive chemotherapy followed by autologous hematopoietic cell transplantation (HCT) or, less often, allogeneic HCT. Unfortunately, many patients will relapse following autologous HCT, and additional therapies are limited [1-4]. Second autologous transplants are difficult because of toxicities, lack of effectiveness, and problems with obtaining hematopoietic stem cells (HSC)

From the [1]Fred Hutchinson Cancer Research Center, Seattle, Washington; [2]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; [3]Rocky Mountain Blood & Marrow Transplantation, Denver, Colorado; [4]Stanford University, Palo Alto, California; [5]University of Leipzig, Leipzig, Germany; [6]University of Torino, Torino, Italy; [7]Oregon Health & Science University, Portland, Oregon; [8]University of Utah, Salt Lake City, Utah; and [9]Intermountain Blood & Marrow Transplant Program, Salt Lake City, Utah

Correspondence and reprint requests: David G. Maloney, MD, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MS D1-100, Seattle, WA 98109 (e-mail: dmaloney@fhcrc.org).

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for transplantation. Allogeneic transplants are appealing because of the potential graft-versus-lymphoma (GVL) effects and a tumor-free graft. Initial studies using myeloablative allogeneic HCT in patients who have relapsed after autologous HCT found high nonrelapse mortality (NRM) [5,6]. More recently, Freytes et al. [7] reported a treatment-related mortality (TRM) of 22% for patients with HL or non-Hodgkin lymphoma (NHL), and Devetten et al. [8] reported Center for International Blood and Marrow Transplant Research (CIBMTR) registry data demonstrating a lower risk of TRM with nonmyeloablative (relative risk [RR] 0.52, 95% confidence interval [CI], 0.26-1.05) and reduced-intensity conditioning (RIC) (RR 0.58, 95% CI, 0.31-1.07) regimens compared to myeloablative regimens; however, this did not reach statistical significance. Allogeneic HCT after nonmyeloablative or RIC has also been used as a treatment option for patients with progressive HL who have failed autologous HCT [9-14]. Importantly, disease responses were seen in the setting of decreased NRM.

Based on preclinical studies in the canine model at the Fred Hutchinson Cancer Research Center (FHCRC), a nonmyeloablative preparative regimen consisting of 2 Gy total body irridiation (TBI) with or without Flu followed by postgrafting immunosuppression with mycophenolate mofetil (MMF) and a calcineurin inhibitor (cyclosporine) was developed [15]. This regimen has proved to be minimally toxic, well tolerated, and potentially effective for patients with malignant or nonmalignant hematologic diseases who were ineligible for conventional HLA-matched related or unrelated donor HCT [16-23].

However, many patients do not have HLA-matched related or unrelated donors. Several studies have described myeloablative HCT using related HLA-haploidentical donors as a viable treatment option for patients with hematologic malignancies; however, inferior survivals were often seen because of increased graft failure/rejection and other significant toxicities including graft-versus-host diseaese (GVHD) [24,25]. To enable HLA-haploidentical HCT after nonmyeloablative conditioning, investigators at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) of Johns Hopkins University expanded upon the FHCRC approach described above by incorporating high-dose, posttransplantation cyclophosphamide (cy) to achieve the selective depletion of alloreactive T cells [26-29]. Specifically, no immunosuppressive drugs were given for the first 3 days following marrow transplant to allow for expansion of alloreactive clones of T cells, which were then killed by administration of a dose of cyclophosphamide (cy). Afterward, immunosuppressive therapy with tacrolimus and MMF was begun both for control of rejection and GVHD. This regimen has been shown to be effective in establishing engraftment with reduced toxicities in high-risk patients with hematologic malignancies [30-33].

Historically, donor type has correlated with outcome, with HLA-matched related grafts having superior outcomes to unrelated and HLA-haploidentical related grafts. Here we evaluated the utility of allogeneic HCT from either HLA-matched related, unrelated, or HLA-haploidentical related donors after nonmyeloablative conditioning as treatment for 90 patients with HL who were ineligible for high-dose conventional allogeneic HCT.

PATIENTS AND METHODS

Eligibility Criteria

This retrospective analysis included data from all patients with HL who received HCT from HLA-matched related (n = 38), unrelated (n = 24), or HLA-haploidentical related (n = 28) donors between December 1998 and October 2007. Results were analyzed as of March 2008. Patients were treated at 12 centers on multi-institutional protocols that were approved by the institutional review boards of the FHCRC and each collaborating center. All patients signed consent forms approved by the local institutional review boards. Patients with a diagnosis of HL who were ineligible for or had failed autologous HCT were included. No exclusions were made for disease status or chemotherapy sensitivity.

Characteristics at HCT

Details regarding patient characteristics are provided in Table 1. Patients received a median number of 5 preceding regimens. Most had preceding local radiation therapy (83%) and had failed high-dose autologous/syngeneic HCT (92%). One candidate for an HLA-haploidentical related graft had failed myeloablative allogeneic HCT. Seven patients (4 HLA-matched related, 3 unrelated) had planned autologous HCT before allogeneic HCT to reduce disease burden.

Patients were designated to be in complete remission (CR) if they had no identifiable disease on computerized tomography (CT) scan ± positron emission tomography (PET) scan, in partial remission (PR) if their disease had decreased by 50% following salvage therapy, in untested relapse if they had relapsed following salvage therapy, and as having refractory disease if they did not respond to or progressed despite salvage therapy. The patients' disease burdens were categorized as either ≥5 cm or <5 cm of tumor mass/lymphadenopathy. Comorbidities were assessed using the HCT-Comorbidity Index (HCT-CI) [34].

Table 1. Patient and Disease Characteristics (n = 90)

Characteristics	HLA-Matched Related (n = 38)	Unrelated (n = 24)	HLA-Haploidentical Related (n = 28)
Age			
Median, in years (range)	33 (17-64)	28 (20-45)	32 (14-62)
Sex, n (%)			
Male	20 (53%)	12 (50%)	13 (46%)
Female	18 (47%)	12 (50%)	15 (54%)
CMV serostatus, n (%)			
Recipient (–) /Donor (–)	18 (47%)	6 (25%)	10 (36%)
Recipient (+) /Donor (–)	6 (16%)	7 (29%)	4 (14%)
Recipient (–) /Donor (+)	4 (11%)	5 (21%)	6 (21%)
Recipient (+) /Donor (+)	10 (26%)	6 (25%)	8 (29%)
Time diagnosis – allogeneic HCT			
Median, in years (range)	3 (1-34)	3 (1-17)	3 (1-18)
Prior treatment			
Median lines of treatment (range)	4 (2-9)	5 (3-10)	5 (3-10)
Local radiotherapy, n (%)	32 (84%)	22 (92%)	21 (75%)
Prior autologous HCT, n (%)			
Failed	34 (89%)*	24 (100%)*	25† (89%)
Time from autologous to allogeneic HCT			
Median, in months (range)	15 (4-110)	20 (8-144)	18† (5-73)
HCT-CI score, n (%)			
0-1	14 (37%)	6 (26%)	11 (39%)
2+	24 (63%)	17 (74%)	17 (61%)
Disease bulk at HCT, n (%)			
<5 cm	32 (89%)	20 (87%)	24 (86%)
>5 cm	4 (11%)	3 (13%)	4 (14%)
Disease status at HCT, n (%)			
CR	11 (29%)	5 (21%)	6 (21%)
PR	16 (42%)	8 (33%)	6 (21%)
Untested relapsed	3 (8%)	2(8%)	4 (14%)
Refractory	8 (21%)	9 (38%)	12 (43%)
Cell dose/kg, median (range) ‡			
CD34 cells ($\times 10^6$)	9.8 (2.8-43)	7.7 (2.3-25)	4.2 (1.7-16.2)
CD3 cells ($\times 10^8$)	4.0 (1.0-68)	2.9 (0.8-10.7)	0.4 (0.2-0.8)

HCT indicates hematopoietic cell transplantation; HCT-CI, HCT-Comorbidity Index; CMV, cytomegalovirus.
*Planned tandem autologous/allogeneic HCT–related (n = 4), unrelated (n = 3).
†One candidate for an HLA-haploidentical related graft had failed myeloablative allogeneic HCT.
‡Graft composition was the only statistically significant difference between the groups.

HLA Matching

Patients and their donors were typed for HLA-A, -B, or -C by at least intermediate-resolution DNA typing, and -DRB1 and -DQB1 by high-resolution techniques [35]. Five unrelated recipient/donor pairs had single HLA-A, -B, or -C antigen mismatches. Of these, 2 also had an additional HLA-A or -B allele mismatch each. One additional unrelated recipient/donor pair had a single HLA-B allele mismatch. For the HLA-haploidentical related donors, the median number of mismatches both in the graft-versus-host (GVH) and host-versus-graft (HVG) directions was 4.

Preparative Regimens and Postgrafting Immunosuppression

The nonmyeloablative preparative regimen consisted of either 2 Gy TBI (7 cGy/min; day 0) alone (n = 17, HLA-matched related) or combined with fludarabine 30 mg/m^2/day (days −4 to −2 [n = 21, HLA-matched related; all unrelated]) followed by postgrafting immunosuppression with MMF or cyclosporine/tacrolimus as previously described [16,22,36]. The 5 patients who received a 1 HLA antigen mismatched unrelated graft received slightly longer courses of MMF (45 mg/kg/day; days 0 to +100 then taper) and cyclosporine (days −3 to day +180 then taper). The nonmyeloablative regimen for the 28 HLA-haploidentical related recipients consisted of cy (14.5 mg/kg/day; days −6, −5), fludarabine (30 mg/m^2/day; days −6 to −2), and 2 Gy TBI (7 cGy/min; day −1). On day +3 (FHCRC) or on days +3 and +4 (SKCCC), cy (50 mg/kg/day) was given, followed by additional postgrafting immunosuppression with tacrolimus (targeted to a level of 5-15 ng/mL; day +4 through day +84, then taper to day 180 [FHCRC] or day +5 through day 180 [SKCCC]) and MMF (45 mg/kg/day; day +4 [FHCRC] or +5 [SKCCC] to day +35). All HLA-haploidentical related recipients received filgrastim (Neupogen, Amgen, Thousand Oaks, CA), 5 μg/kg/day by subcutaneous injection starting on day +1 (SKCCC) or day +4 (FHCRC), until the absolute neutrophil counts (ANC) were >500/μL for 3 days.

Collection of Hematopoietic Cells and Supportive Care

All HLA-matched related and unrelated recipients received granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood mononuclear cells (PBMC) as the stem cell product, whereas all HLA-haploidentical related recipients received bone marrow. Supportive care practices were per local center practice guidelines [37,38].

GVHD Grading and Treatment

Diagnosis, clinical grading, and treatment of acute and chronic GVHD (aGVHD, cGVHD) were done as previously described [39-42].

Analyses of Donor Chimerism

Donor engraftment was confirmed by chimerism analyses [43-46]. Rejection was defined as the detection of ≤5% donor T cells (CD3) for HLA-matched related, unrelated, and HLA-haploidentical related (FHCRC) recipients and <5% donor cells after HCT for the HLA-haploidentical related recipients at SKCCC.

Statistical Methods

Overall (OS) and progression-free survival (PFS) were estimated by the Kaplan-Meier method. Cumulative incidence estimates were calculated for relapse, NRM, and aGVHD and cGVHD. Hazard ratios comparing rates of events between groups and adjusting for other risk factors were estimated from Cox regression models. All models were adjusted for disease burden ≥5 or <5 cm tumor mass/lymphadenopathy, disease status at HCT (in CR, PR, or untested relapse/refractory), and HCT-CI (0-1 versus ≥2).

RESULTS

Engraftment

The median absolute neutrophil nadirs for HLA-matched related, unrelated, and HLA-haploidentical related recipients were 672 (range: 0-3460), 400 (range: 0-1450), and 0 (range: 0-140) cells/μL and occurred at medians of 14 (range: 7-96), 12 (range: 3-93), and 9 (range: 1-14) days, respectively.

Median percentages of peripheral blood donor CD3+ T cell chimerism at days 28, 56, and 84 were 92%, 94%, and 95% for HLA-matched related recipients and 95%, 98%, and 99% for unrelated recipients. Median percentages of chimerism at 1 and 2 months after HCT were 100 and 100, respectively for the HLA-haploidentical related recipients. None of the 90 patients rejected their grafts.

Sixty-six percent HLA-matched related, 75% unrelated, and 93% HLA-haploidentical related recipients required red blood cell transfusions, and the median number of red blood cell units given were 6 (range: 1-24), 6 (range: 2-21), and 4 (range: 2-17), respectively. In addition, 32% HLA-matched related, 33% unrelated, and 82% HLA-haploidentical related recipients required platelet transfusions, and the median number of platelet transfusions given were 7 (range: 1-16), 4 (range: 1-23), and 15 (range: 2-100), respectively.

GVHD

The incidences of aGVHD grades II-IV and III-IV were 50% and 16% (HLA-matched related), 50% and 8% (unrelated), and 43% and 11% (HLA-haploidentical related) (Figure 1A and B and Table 2). With a median follow up of 25 (range: 4-87) months for living patients; the 2-year incidences of extensive cGVHD for HLA-matched related, unrelated, and HLA-haploidentical related recipients were 50%, 63%, and 35%, respectively (Figure 1C). The median days to development of grade II-IV aGVHD and cGVHD were 39 and 154 (HLA-matched related), 28 and 198 (unrelated), and 34 and 177 (HLA-haploidentical related), respectively. When included in a multivariate model that adjusted for disease burden (tumor mass/lymphadenopathy ≥5 cm or <5 cm), HCT-CI (0-1, 2+), and disease status at time of HCT (CR, PR, untested relapse/refractory), there was a trend toward lower incidences of extensive cGVHD in the HLA-haploidentical related recipients compared to the HLA-matched related (hazard ratio [HR] = 0.54, 95% CI [0.2-1.2], $P = .14$) and unrelated (HR = 0.45, 95% CI [0.2-1.0], $P = .06$) recipients. However, multivariate analysis demonstrated that the recipients of HLA-haploidentical related grafts were more successful in discontinuing immunosuppression compared to the HLA-matched related (HR = 2.46, 95% CI [1.0-5.8], $P = .04$) and unrelated (HR = 3.05, 95% CI [1.1-8.1], $P = .03$) recipients.

Disease Response

Of the 11 HLA-matched related, 5 unrelated, and 6 HLA-haploidentical related recipients in CR before HCT, 5, 2, and 1 relapsed after HCT, respectively. Of the patients with measurable disease before HCT, 11/27 (41%) HLA-matched related, 12/19 (63%) unrelated, and 19/22 (86%) HLA-haploidentical related recipients achieved initial CR or PR after HCT; however, 2, 8, and 7 recipients subsequently relapsed or progressed, respectively. One HLA-matched related recipient who was in PR before HCT progressed 1 month after HCT and subsequently entered CR following radiation therapy; CR is sustained now 3.4 years. For patients with measurable disease before HCT who entered CR following HCT, the median times to CR were 86 (range: 55-185), 83 (range: 55-195), and 62 (range: 29-281) days for HLA-matched related, unrelated and HLA-haploidentical related recipients, respectively. In univariate analysis, there were no differences in OS, PFS, or incidences of relapse based on disease status at time of HCT. Of the 11 patients with disease burden ≥5 cm at time of HCT, 4 were in CR (1 HLA-matched related, 3 HLA-haploidentical related), 2 had stable disease, and 5 had relapsed/refractory disease at time of last follow-up.

Disease Progression

The 2-year cumulative incidences of relapse/disease progression were 56% (HLA-matched related), 63% (unrelated), and 40% (HLA-haploidentical related) (Figure 2 and Table 2). There were significantly decreased risks of relapse for HLA-haploidentical related recipients compared to HLA-matched related (HR = 0.35, 95% CI [0.2-0.8], $P = .01$) and unrelated (HR = 0.43, 95% CI [0.2-0.9], $P = .03$) recipients. There were no differences in risks of relapse between HLA-matched related and unrelated recipients. The median times to relapse/progression for the HLA-matched related, unrelated, and HLA-haploidentical

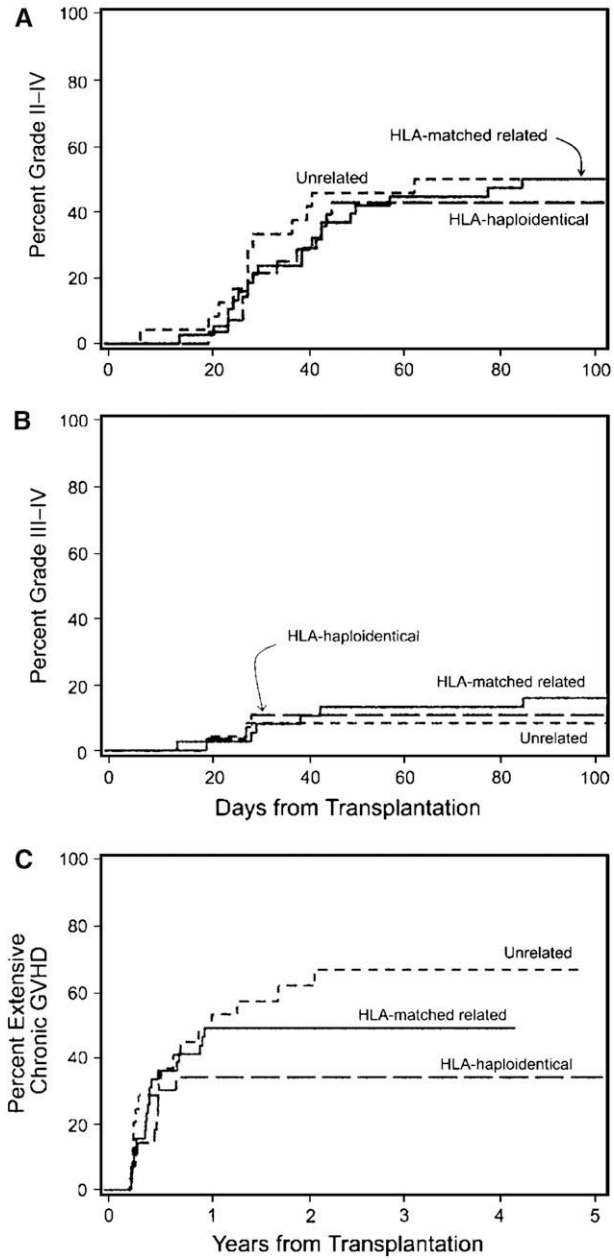

Figure 1. Incidences of (A) grade II-IV aGVHD, (B) grade III-IV aGVHD, and (C) extensive cGVHD according to donor type.

related recipients were 119 (range: 29-2632), 279 (range: 4-849), and 164 (range: 28-1069) days, respectively. Six HLA-matched related and 4 unrelated recipients with disease relapse/progression failed to respond to donor lymphocyte infusion (DLI). One HLA-haploidentical related recipient with disease progression received DLI × 3 and is alive in CR 4.8 years after HCT.

Survival and NRM

The 2-year OS and PFS were 53% and 23% (HLA-matched related), 58% and 29% (unrelated), and 58% and 51% (HLA-haploidentical related), respectively after HCT (Figure 3A and 3B, and Table 2). Although multivariate analysis did not demonstrate any significant differences in OS between the 3 groups, significantly improved PFS was found for HLA-haploidentical related recipients compared to HLA-matched related (HR = 0.30; 95% CI [0.1-0.6], P = .0008) and unrelated (HR = 0.46, 95% CI [0.2-0.9], P = .03) recipients. There were no significant differences in PFS among HLA-matched related compared to the unrelated recipients. Day 200 and 2-year NRM were 16% and 21% (HLA-matched related), 0% and 8% (unrelated), and 0% and 9% (HLA-haploidentical related). NRM was significantly lower for HLA-haploidentical related (HR = 0.14, 95% CI [0.0-0.7], P = .02) recipients compared to HLA-matched related recipients (Figure 4). Although not significant, there

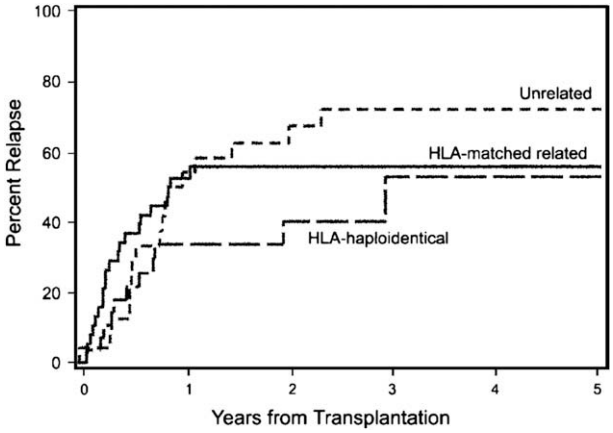

Figure 2. Incidences of relapse according to donor type.

was a trend toward lower NRM for unrelated recipients (HR = 0.23, 95% CI [0.0-1.2], $P = .08$) compared to related recipients. There were no significant differences in NRM between the unrelated and HLA-haploidentical related recipients. The primary causes of NRM for all 3 groups were GVHD ± infections (6/8 HLA-matched related, 2/2 unrelated, 2/2 HLA-haploidentical related recipients).

DISCUSSION

Successful treatments in patients with HL who have relapsed or refractory disease after autologous HCT are limited, and outcomes have been poor. Second HCT using myeloablative conditioning has been associated with high NRM and relapse rates with only small numbers of patients achieving long-term remissions and cures. Here we compared outcomes of high-risk patients with HL who received nonmyeloablative conditioning before HLA-matched related, unrelated, or HLA-haploidentical related grafts. Most patients were heavily pretreated, and had failed both high-dose autologous HCT and local radiation therapy. The 3 patient groups had similar distributions of HCT-CI scores. However, more unrelated and HLA-haploidentical related recipients had relapsed or refractory disease compared to HLA-matched related recipients.

We found no significant differences in OS among the 3 groups. However, day 200 and 2-year NRM were lowest among unrelated and HLA-haploidentical related recipients. Although "higher," the NRM for the HLA-matched related group was actually similar to our experience in patients with aggressive non Hodgkin lymphoma [47,48] and other hematologic malignancies [20]. In contrast, the NRM seen in recipients of alternative donor grafts was unexpectedly low compared to what has been previously seen in larger studies [20,33]. This finding could be because of the small numbers of patients studied.

Table 2. Outcomes by Donor Type

	HLA-Matched Related (n = 38)	Unrelated (n = 24)	HLA-Haploidentical related (n=28)
Follow-up for surviving patients			
Median, in months (range)	24 (11-87)	38 (20-60)	22 (4-62)
GVHD			
Acute	50%	50%	43%
Grade II-IV			
Grade III-IV	16%	8%	11%
2-Year extensive chronic	50%	63%	35%
Day 200 NRM	18%*	0%	0%
2-year			
Overall survival	53%	58%	58%
NRM	21%*	8%	9%
Relapse/progressive disease	56%	63%	40%*
PFS	23%	29%	51%*

PFS indicates progression-free survival; NRM, nonrelapse mortality; GVHD, graft-versus-host disease.
*Adjusted hazard ratio analysis demonstrated statistically significant differences (see text).

We also found no differences in the incidences of severe grade III-IV aGVHD or cGVHD between the groups. Despite greater HLA-disparity in the HLA-haploidentical related recipients, the incidences of severe aGVHD and extensive cGVHD were quite

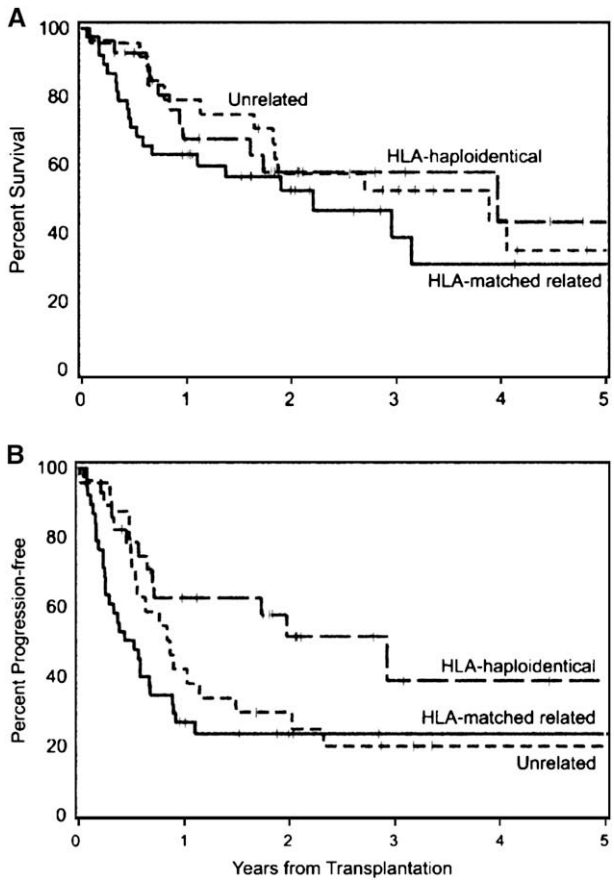

Figure 3. Incidences of (A) OS, and (B) PFS according to donor type.

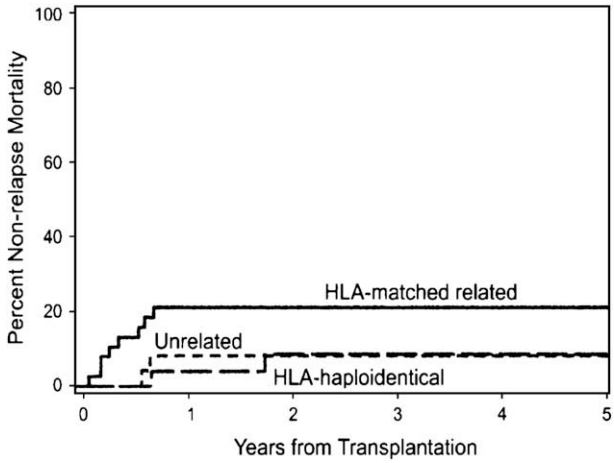

Figure 4. Incidences of NRM according to donor type.

similar to what has been reported with other reduced-intensity regimens using HLA-matched related and unrelated donors, supporting the hypothesis that post-transplantation Cy is important in killing T cell clones that are involved in the development of GVHD [49]. However, it should also be noted that HLA-haploidentical related recipients received bone marrow, which generally causes less cGVHD compared to PBSC, which was the stem cell product among HLA-matched related and unrelated recipients [50-52].

We also found lower rates of relapse and better PFS at 2 years for the HLA-haploidentical related recipients. The greater antitumor effects noted in the HLA-haploidentical related group may in part be due to the slightly increased intensity of the conditioning regimen and in part, because of the HLA disparity and, thereby greater GVL effects. However, the same was not true for the unrelated donor group who actually had slightly higher rates of relapse at 2 years compared to the HLA-matched related group. Although there were more patients in both the unrelated and HLA-haploidentical related groups with relapsed/refractory disease before HCT, we did not find a difference in outcome based on disease status to account for the differences in relapse.

Several groups of investigators have reported on the use of nonmyeloablative/reduced intensity conditioning (RIC) regimens with HLA-matched related or unrelated grafts for treatment of relapsed/refractory HL. Direct comparisons between studies are difficult given the heterogeneity of the patient populations and preparative regimens used; however, several points are worth discussing. Peggs et al. [14] published results on 49 patients conditioned with Flu, Mel and alemtuzumab and compared outcomes based on donors (HLA-matched related or unrelated). Day 100 and 2-year NRM were low (4% and 16%, respectively). Disease relapse/progression occurred in 43% of patients and 33% required DLI because of progressive disease. The projected 4-year PFS was 32%. Anderlini et al. [9] reported on 40 patients who were primarily conditioned with a combination of either Flu and Cy ± ATG, or Flu and Mel, followed by HLA-matched related or unrelated grafts. With a median follow-up of 13 months, the 18-month OS, incidences of relapse, and PFS were 61%, 55%, and 32%, respectively. Day 100 and 18-month TRM were 5% and 22%, respectively. In contrast to our study, all patients enrolled had chemosensitive or stable disease after salvage therapy; those with progressive disease were treated off protocol that may have contributed to the slightly better PFS seen in their study. Anderlini et al. [53] published an update on Flu/Mel group (n = 58) and found similar OS (64%), disease relapse/progression (55%), and PFS (32%) at a longer follow-up (median 2 years).

Recently, Majhail et al. [54] reported on 21 patients with HL who were conditioned with either busulfan (Bu), Flu, and 2 Gy TBI, or Cy, fludarabine, and 2 Gy TBI, followed by either HLA-matched sibling (n = 12) or unrelated umbilical cord blood (UCB; n = 9) grafts. With a median follow-up of 17 (UCB) and 24 (HLA-matched sibling) months, the 2-year OS and PFS were 51% and 25% (UCB) and 48% and 20% (HLA-matched sibling), respectively. Day 180 treatment related mortality (TRM) were 22% (UCB) and 25% (HLA-matched sibling).

RIC/nonmyeloablative conditioning regimens have expanded treatment options for very advanced high-risk patients with HL. Importantly, our results and those of others demonstrated significant decreases in both early and late NRM compared to HCT using myeloablative regimens. Our data suggest that salvage allogeneic HCT using nonmyeloablative conditioning provides antitumor activity in patients with very advanced disease. Importantly, alternative donor sources are a viable option particularly for those patients who may have a limited window of opportunity to proceed to HCT. Similar to what others have reported, relapse/progression continues to be the major problem regardless of stem cell source in these heavily pretreated patients. Inclusion of agents that more specifically target HL is needed. Possibilities include anti-CD30 antibodies or antibody/drug conjugates, histone deacetylase inhibitors, or radiolabeled antibodies [55]. Ultimately, separation of GVHD activity from graft-versus-tumor responses through the identification of minor antigen polymorphisms or tumor specific antigens is needed to provide safer and more effective therapy.

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